Remarks

Introductory Comments:

Claims 1-9, 29, 36 and 37 were examined in the Office Action dated May 27, 1998 and rejected under 35 USC §103, as obvious. These rejections are believed to be overcome in part by the above amendments and are otherwise traversed for the reasons discussed below. Applicants acknowledge and appreciate the withdrawal of the previous 35 U.S.C. §102(b) rejections over Idson and Mizushima.

Overview of the Above Amendments:

Claim 1 has been amended, per the Examiner's suggestion, to recite "consisting essentially of" instead of "comprising." Claim 37 has been amended to an independent form and recites an adjuvant composition consisting essentially of a metabolizable oil, an emulsifying agent and a selected antigen. Support for the amendment can be found throughout the specification at, e.g., page 4, lines 30-31; page 24, lines 15-18; page 25, lines 7-13; page 28, lines 5-6; and in the examples.

Thus, no new matter has been added to the application by way of the amendment.

Rejections Over the Art:

The Office maintained the rejection of claims 1-9, 29 and 36 under 35 USC §103(a), as unpatentable over U.S. Patent No. 5,109,026 to Hoskinson et al. ("Hoskinson") and U.S. Patent No. 3,919,411 to Glass et al. ("Glass") in view of Idson and *Remington's Pharmaceutical Sciences* (Gennaro, ed.) Mack Publishing Co., Pennsylvania, pp. 298-299, 317-321 and 1507-1511, 1985 ("Remington"), for reasons of record.

However, the Office indicated that amending claims 1 and 37 to recite "consisting essentially of" would

distinguish over Glass and Hoskins, and the rejection would be withdrawn. Office Action, page 4. Although applicants believe the claims already distinguish over the art, claims 1 and 37 have been amended as suggested by the Office in order to advance prosecution. Thus, applicants respectfully request withdrawal of the rejection under 35 USC §103(a) over Hoskinson and Glass.

Further, the Office alleges that it is not possible to determine the exact composition of "MF59" based solely on the specification. In support of this allegation, the Office asserts that "there is an inconsistency in terminology within the specification and between the declaration and the specification." Office Action, pages 4-5, bridging paragraph. Applicants rebut the Office's assertion, and reiterate that the composition of "MF59" is indeed ascertainable for reasons of record. However, in order to expedite the prosecution, applicants are submitting a supplemental declaration to clarify the "apparent discrepancies" i.e. that the MF59 referred to in the Declaration submitted on May 14, 1997 is the same as the composition referred to as MF59 in the specification.

The Office also rejected claims 1-9, 29 and 36 under 35 U.S.C. 103(a) as being unpatentable over Woodard et al., *Vaccine* 3:137-145 (1985) ("Woodard"), in view of Silvestri et al., *International Journal of Pharmaceutics*, 50:141-146 (1989) ("Silvestri"). In support of this rejection, the Office asserts that Woodard discloses an adjuvant composition comprising a metabolizable oil, and an emulsifying agent, wherein the composition exists in the absence of a polyoxypropylene-polyoxyethylene block copolymer and a muramyl peptide. Although, the Office acknowledges that Woodard does not specifically disclose that "substantially all" of the droplets are less than 1

micron in diameter, the Office asserts that Woodard's droplets appear to be "much smaller than 2.5 mm calibration line in Figure 2(A)." Further, the Office alleges that Woodard's disclosure stating small droplet size is a desirable feature for a stable emulsion and would provide motivation for stabilizing emulsion compositions by making the droplet size as small as possible. Additionally, the Office asserts that Silvestri also discloses the desirability of submicron size droplets for improved stability of oil-in-water emulsions. Thus the Office concludes that it would have been obvious to one of ordinary skill in the art to make and to use an adjuvant in the form of an oil-in-water emulsion, comprising a metabolizable oil and an emulsifying agent, wherein substantially all the oil droplets are less than 1 micron in diameter and the composition exists in the absence of block copolymer and muramyl peptide. Office Action, pages 6-7. However, applicants do not agree that the combination of Woodard with Silvestri renders the present claims obvious.

Case law provides that a prior art reference must be considered in its entirety, and that distilling the invention to a "gist" or "thrust" of an invention disregards the "as a whole" requirement. Further, a prior art reference must be considered in its entirety, including portions that would lead away from the claimed inventions. (*W.L. Gore & Associates, Inc., v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983). Even when references relied upon teach that all aspects of the claimed invention are known individually in the art, *prima facie* obviousness is not established without some objective reasoning to combine the teachings of the references (*Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993)).

Applicants respectfully submit that the invention as a whole is not obvious and that there is no suggestion to combine the teachings of the art as asserted. In particular, claims 1-9, 29 and 36, as amended, pertain to an adjuvant composition consisting essentially of an oil-in-water emulsion having oil droplets substantially all of which are less than 1 micron in diameter and wherein said composition exists in the absence of any polyoxypropylene-polyoxyethylene block copolymer, and further wherein the adjuvant composition is capable of increasing the immune response to the antigenic substance when administered with the antigenic substance.

Although Woodard discloses the desirability of submicron droplets for improved stability, it teaches that the stability of the oil-in-water emulsions does not affect the antibody response. Thus, Woodard does not suggest or imply that in order to increase the immunological activity, substantially all of the droplets in the adjuvant composition must be less than 1 micron in size. Further, Woodard discloses that use of emulsifiers may be detrimental to the immune response, and that considerable experimentation is involved in vaccine emulsion technology (page 142). Thus, Woodard actually teaches away from applicants' claimed invention.

Further, while Silvestri discloses the desirability of submicron size droplets to achieve improved stability in oil-in-water emulsions, the reference does not suggest immunological adjuvant compositions in the form of oil-in-water emulsion having droplets wherein substantially all of the droplets are less than 1 micron in diameter. Thus even when considering Silvestri in its entirety, it does not cure the deficiencies of Woodard. There is absolutely no suggestion in either of Woodard or Silvestri that

formulations described therein could be modified to render applicants' unique compositions. Additionally, there is absolutely no indication that doing so would be successful for producing an adjuvant composition as claimed.

Therefore, although the references cited by the Office disclose bits and pieces of the claimed invention, there is no suggestion or incentive to combine Woodard with Silvestri. Such combination is therefore inappropriate.

Thus, applicants submit that the claimed invention is nonobvious over the art and request reconsideration and withdrawal of this ground of rejection.

Conclusion

Applicants respectfully submit that the claims as amended define an invention which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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Currently Pending Claims

1. (Six times amended) An adjuvant composition consisting essentially of:

(1) a metabolizable oil and

(2) an emulsifying agent, wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are less than 1 micron in diameter and wherein said composition exists in the absence of any polyoxypropylene-polyoxyethylene block copolymer and in the absence of any muramyl peptide, and further wherein said adjuvant composition is capable of increasing the immune response to an antigen when administered with the antigen.

2. The composition of Claim 1, wherein said oil is an animal oil.

3. The composition of Claim 2, wherein said oil is an unsaturated hydrocarbon.

4. The composition of Claim 1, wherein said oil is a terpenoid.

5. The composition of Claim 1, wherein said oil is a vegetable oil.

6. The composition of Claim 1, wherein said composition comprises 0.5 to 20 % by volume of said oil in an aqueous medium.

7. The composition of Claim 1, wherein said emulsifying agent comprises a non-ionic detergent.

8. (Amended) The composition of Claim 1, wherein said emulsifying agent comprises a polyoxyethylene sorbitan mono-, di-, or triester or a sorbitan mono-, di-, or triester.

9. (Amended) The composition of Claim 8, wherein said composition comprises .02 to 2.5 % by weight of said emulsifying agent.

29. (Thrice amended) A method of stimulating an immune response in a host animal comprising:

administering an antigen to said animal in the presence of an immunostimulating amount of an adjuvant composition of claim 1.

36. The composition of Claim 1 wherein said emulsifying agent comprises a polyoxyethylene sorbitan mono-, di-, or triester and a sorbitan mono-, di-, or triester.

37. (Amended) An adjuvant composition consisting essentially of:

(1) a metabolizable oil;

(2) an emulsifying agent, wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are less than 1 micron in diameter and wherein said composition exists in the absence of any polyoxypropylene-polyoxyethylene block copolymer and in the absence of any muramyl peptide, and further wherein said adjuvant composition is capable of increasing the immune response to an antigen when administered with the antigen; and

(3) a selected antigen.